fibroplasia, and rubeosis; cardiovascular diseases; cerebral vascular diseases; diabetes-associated diseases; and immune disorders including chronic inflammation and autoimmunity.

90. (new) The method of claim 80 wherein the angiogenic disease is selected from the group consisting of neoplastic diseases including tumors and tumor metastasis; benign tumors including hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyrogenic granulomas; connective tissue disorders including rheumatoid arthritis and atherosclerosis; ocular angiogenic diseases including diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, and rubeosis; cardiovascular diseases; cerebral vascular diseases; diabetes-associated diseases; and immune disorders including chronic inflammation and autoimmunity.

REMARKS

The amendments and remarks made herein place the claims in condition for allowance or better form for appeal. New claims 89 and 90 have been added. The new claims are fully supported by the specification and do not constitute new subject matter as defined in 35 U.S.C. § 132. Specifically, claims 89 and 90 are supported by the specification at p. 18, *ll.* 13-21.

A copy of the claims that will be pending upon entry of the instant amendment is attached hereto as Exhibit A. Applicants respectfully request that the addition of the new claims herein be entered into the file of the above-identified application and that the remarks herein be fully considered.

1. The Rejection Under 35 U.S.C. §112 First Paragraph, Should Be Withdrawn

Claims 19-21 and 23-24 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The gravamen of the Examiner's rejection is that it is unpredictable whether the administration of a plasminogen activator alone or in combination with a sulfhydryl donor would be adequate for inhibiting angiogenesis *in vivo* in light of Berman *et al.* 1982, Invest. Opthamal. Vis. Sci. 22:191-199 ("Berman"). According to the Examiner, Berman shows the opposite effect -- *i.e.*, that the administration of urokinase (a plasminogen activator) actually promotes vascularization of the cornea *in vivo*. This rejection is in error and should be withdrawn.

Berman is irrelevant to enablement of the method of the invention because Berman does not use the claimed protocol -- *i.e.*, Berman does not administer a "therapeutically effective amount" of plasminogen activator that increases the amount of

angiostatin in the animal.[1] Instead, Berman injects 20µl aliquots of urokinase (3.7 CTA Units) intrastromally into the corneas of 2 to 3.5 kg rabbits (as a bleb about 2 mm on the center from the limbus of contralateral corneas). In contrast, Applicants claim the administration of an amount of plasminogen activator *effective to increase the amount of angiostatin* in the animal to treat the angiogenic disease.

By contrast to the protocol used by Berman, when plasminogen activator is administered in accordance with the claimed methods of the present invention, the amount of angiostatin generated *in vivo* will increase and thereby inhibit angiogenesis. Moreover, Applicants have demonstrated that angiostatin inhibits angiogenesis in corneas. See, for example, Reference BS of record, co-authored by the inventor (Gately et al., 1996, Cancer Res. 56: 4887-90, at Fig. 3 and its accompanying discussion at p. 4889, col. 1, last paragraph bridging over to col. 2)[2], which demonstrates that angiostatin is indeed effective in inhibiting angiogenesis in the cornea. Thus, the Examiner cannot properly rely on Berman to show unpredictability of the claimed method, because Berman's protocol does not use the claimed method.[3]

The present invention is fully enabled because it discloses and claims methods of increasing the amount of angiostatin present in an animal to prevent or inhibit angiogenesis (including angiogenesis of any and all angiogenic diseases) by generating angiostatin via the administration of a therapeutically effective amount of plasminogen activator. The Examiner's contention that Applicants have demonstrated efficacy only for combinations of plasminogen activator with a sulfhydryl donor for the treatment of cancer (Office Action, p. 4) is incorrect. In this regard, the Examiner's attention is invited to the following evidence of record in parent application Serial No. 08/991,761, which the Examiner agreed establishes the following facts: (1) Urokinase alone generates angiostatin in human plasma (Soff Supplemental Declaration dated December 4, 2001, Exhibit 5); (2) Urokinase alone generates angiostatin in human patients (Soff Supplemental Declaration dated February 13, 2001, paragraphs 9, 14, 18 & Exhibit D); (3) the generation of angiostatin has a clinical benefit in human patients with malignant neoplastic disease (Soff Supplemental Declaration dated February 13, 2001, Exhibit B); and (4) when administered without a sulfhydryl donor, the dose and dosage regimen of plasminogen activator can be adjusted to generate levels of angiostatin that have a clinical benefit in patients with malignant neoplastic disease (Second Supplemental Declaration of Gerald A. Soff, M.D., Under 37 C.F.R. § 1.132, dated October

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[1] In fact Berman does not disclose or suggest the generation of any angiostatin.

[2] Reference BS was published subsequent to the September 17, 1996 priority date of the present application.

[3] The Examiner's reliance of Volpert is even less relevant to enablement. Volpert relates to the use of captopril alone. The Applicant has already demonstrated, and the Examiner does not dispute, that combinations of plasminogen activator and captopril inhibit angiogenesis. See ensuing discussion above.

7, 2002). For the Examiner's convenience, copies of the Soff Declarations referred to above are enclosed herewith as Exhibit B.

In view of the foregoing, the rejection under 35 U.S.C. § 112 should be withdrawn. Thus, Applicants have demonstrated that using the method of the invention, angiostatin is generated in patients, and has a clinical benefit in treating cancer. The Examiner has not supplied any evidence or reason to doubt that such generation of angiostatin in patients would likewise have a clinical benefit in other angiogenic diseases.

In the event that there are any facts relied upon for rejecting any of the pending claims within the personal knowledge of the Examiner or an employee of the United States Patent and Trademark Office, Applicants respectfully request that the Examiner or such employee submit an affidavit attesting to such personal knowledge pursuant to 37 C.F.R. § 1.104(d)(2).

2. Rejection Under Obviousness-Type Double Patenting

The Examiner has rejected claims 19, 20, and 23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 65-68 of pending U.S. Application No. 08/991,761. Applicants note with appreciation the Examiner's indication that this rejection will be held in abeyance until the claims are otherwise deemed allowable at which time Applicants will file a terminal disclaimer, if appropriate, based on the final version of the claims allowed.

The Examiner notes that the application contains claims drawn to an invention nonelected with traverse and that such claims should be canceled. Applicants continue to respectfully traverse the restriction requirement and believe the restriction requirement is improper.

CONCLUSION

Entry and consideration of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Applicants believe that the present claims meet all of the requirements for patentability. If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-6431.

Respectfully submitted,

Date: April 17, 2003

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Enclosures